Exhibit I

Note of Caution: Study Raises Specter Of Cardiovascular Risk For Hot Arthritis Pills --- Vioxx and Celebrex Marketers Dispute the Research, Sought to Downplay It --- A Spurned Appeal to JAMA

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Byline: By Thomas M. Burton and Gardiner Harris, Staff Reporters of The Wall Street Journal

Body

The blockbuster arthritis drugs Vioxx and Celebrex have had the most successful product launches in pharmaceutical history. The $3-a-day pills together generate $6 billion in annual sales, spurred by the hope that users may be spared the ulcers that older painkillers can cause.

But new research raises the possibility that the breakthrough drugs could have a worse side effect: an increased risk of heart attack.

The research poses the first serious threat to these drugs, which have been used by tens of millions of people world-wide since they came out in 1999. Its release follows an unusual behind-the-scenes push by marketers of the two drugs to lobby the prominent cardiologists who wrote the study and the journal that published it. The cardiologists, for their part, now fault the drug companies for failing to address adequately a potentially serious health concern.

Moreover, a study last year purporting to prove Celebrex's milder effects on the stomach than older remedies now appears exaggerated, because investigators for Pharmacia Corp., which is Celebrex's manufacturer and co-marketer with Pfizer Inc., didn't publish half of the study's data. When the full set of data is crunched, Celebrex looks no better at avoiding ulcers than generic pills costing pennies a day. Merck & Co.'s Vioxx, on the other hand, does show a benefit in avoiding gastrointestinal side effects.

The cardiac concerns appear in an analysis by the noted cardiologists Eric J. Topol and Steven E. Nissen, chairman and vice chairman, respectively, of cardiovascular medicine at the Cleveland Clinic. Their study of Vioxx and Celebrex concludes, "Current data would suggest that use of these so-called `COX-2 inhibitors' might lead to increased cardiovascular events."

Their conclusions, published in today's Journal of the American Medical Association, are generally more critical of Merck's Vioxx. The authors say patients taking Vioxx had more than twice as many heart attacks, strokes and other cardiovascular events as patients getting an older, generic arthritis drug, naproxen. They conclude that Celebrex, too, seems to be associated with a relatively high rate of heart attacks.

The authors stress that their work is a new analysis of Merck's and Pharmacia's own raw data and of other past studies and not a new trial, so their conclusions aren't definitive. The marketers of the drugs and some outside experts dispute the conclusions.

The article also says part of the reason Vioxx didn't stack up as well might be that the drug it was compared with, naproxen, could have a heart benefit. It might prevent blood-clotting, in a fashion similar to aspirin.

The side-effect worries with Vioxx and Celebrex, as well as new problems being associated with popular cholesterol-lowering drugs, result in part from their huge rise in usage. The problems are a reminder that even the safest and most beneficial drugs carry some risks, which are often magnified when a medicine is prescribed for millions of people.

Drs. Topol and Nissen, who collaborated on the research with cardiologist Debabrata Mukherjee, now of the University of Michigan, say they have tried unsuccessfully to persuade the makers of Vioxx and Celebrex to launch new clinical studies of the possible cardiac risks. "The reluctance to move forward is disturbing," Dr. Topol says. "Either they're moving at glacial speed, or they're waiting to see what the fallout will be from this and other reports. We're staring at a major public-health issue."

Merck and Pharmacia say they believe no such clinical study is necessary. First, they say, no heart-attack risk emerged from their research. Moreover, they say research already is under way on Vioxx that should answer any remaining cardiac questions.

"I don't think there are any sound conclusions that can be drawn from this study," says Marvin Konstam, chief of cardiology at New England Medical Center, who is a consultant to Merck. Dr. Konstam says he has done a more extensive analysis of all Merck data on Vioxx and concluded "there is no suggestion of a cardiovascular risk" from the drug.

At Celebrex maker Pharmacia, Steve Geis, group vice president for clinical research, adds: "We have never seen in any of our databases that Celebrex has a higher rate of cardiovascular events."

The companies question the cardiac study's methodology, and so do some independent experts. "They have taken data from different prospective trials and rearranged them, and that's a very dubious statistical approach," says Garret FitzGerald, chairman of the University of Pennsylvania's Department of Pharmacology and a longtime expert on this class of drugs. He was co-author of a study of the two drugs published two weeks ago in the New England Journal of Medicine that looked at the same data analyzed in JAMA and came to less-alarming conclusions. "This kind of data manipulation can be very distorting," Dr. FitzGerald says.

Even so, the repercussions from the cardiac study could be significant. One reason is the sterling reputations of the authors and of the Cleveland Clinic, one of the nation's most respected cardiology centers. Another is that purported side-effect advantages were what fueled the growth of these drugs in the first place.

Doctors have long fervently hoped the COX-2 inhibitors might have advantages over older pain pills like the first "miracle" pain drug, aspirin.

Aspirin, found in the inner bark of willow trees, in 1899 established the modern pharmaceuticals industry. But it also turns out to promote ulcers. So do other pain pills such as ibuprofen, naproxen and diclofenac, collectively called non-steroidal anti-inflammatory drugs, or NSAIDs.

All reduce pain and inflammation by inhibiting an enzyme called cyclooxygenase. For years, researchers tried to figure out if they could block that enzyme in the periphery of the body, where most pain is created, without interfering with its protective effect in the gut.

In 1989, Philip Needleman of Washington University in St. Louis postulated there might be two forms of cyclooxygenase: one primarily in the gut and one primarily in the periphery, called cyclooxygenase-2, or COX-2. He moved to Monsanto Co.'s

Searle drug unit -- now owned by Pharmacia -- and spearheaded the search for a molecule that would block solely COX-2. The result was Celebrex, launched in early 1999.

Four months later, Merck brought out its own COX-2 inhibitor, Vioxx.

Both were approved because tests with a scope that was snaked into the stomach showed they produced lower rates of visible ulcer-like lesions. However, although many users believe the drugs produce less stomach pain than older arthritis drugs, no one has ever proved that these visible lesions are indicators of ulcers. So the Food and Drug Administration, in approving the drugs, made the marketers print the same label warning as NSAIDs: that 2% to 4% of those using the drugs for at least a year could get ulcers.

Even so, the drugs caught on because doctors and patients believed they were less likely to cause gastrointestinal problems. To try to prove this belief -- and rid their drugs of the label warning -- the companies undertook larger studies and presented them to an FDA advisory panel in February.

The step backfired. The FDA panel, in an unusual move, published the research on the Internet. This disclosed that Pharmacia had a half year of Celebrex data beyond what it published -- and the full, 12-month trial showed worse results regarding ulcers than did the six months of data published in JAMA. This surprised JAMA editors, who learned that the manufacturer had decided against submitting the full set of data to the journal.

Defending that decision, Jay Goldstein, professor of medicine at the University of Illinois at Chicago and one of the Celebrex study's authors, says the extra data were statistically suspect because a high number of patients dropped out during the study's second six months. The authors worried that JAMA wouldn't publish the study with such suspect data, he says.

But JAMA's editor, Catherine D. DeAngelis, says the company and study authors should have told her about the extra data and allowed the journal to help decide just what to publish. "I was very upset when I found out that they had a full year's data," she says.

As FDA officials combed through all the data, say people familiar with the events, they also grew concerned about the apparently high rate of cardiac events, especially in Merck's data on Vioxx. The agency enlisted Dr. Nissen to assist with the FDA arthritis advisory committee's evaluation of the heart data. He soon grew concerned that Merck and its own clinical investigators hadn't, in his view, sufficiently emphasized the cardiac issue.

This wasn't a trifling worry. Millions of older people -- those most prone to heart disease -- take these arthritis drugs. So Drs. Nissen and Topol decided to air the issue. "We asked, `What's going on here? Are these companies being forthright?' " Dr. Topol recalls. "I wouldn't say this was buried, but the appropriate cautionary flag wasn't raised."

Merck sought to downplay the cardiac issue -- in meetings in New York and Cleveland with Cleveland Clinic doctors, in e-mails and in phone calls to the Cleveland doctors and the editor of JAMA. Pfizer also sought to minimize the issue in phone calls from one of its senior scientists, Mitchell Gandelman, to the Cleveland Clinic, according to one person familiar with the events. Laura Demopoulos, who is Merck's senior director of cardiovascular clinical research, and Alise Reicin, a senior director of clinical research, met with Dr. Topol in Cleveland. Dr. Reicin and Peter DiBattiste, Merck director of cardiovascular clinical research, met with Dr. Nissen in New York.

"We were trying to provide background," says Dr. Demopoulos. This included data provided to the FDA and since published from 19 studies and 28,000 patients comparing Vioxx with placebos and NSAIDs. She says these data show no increase in cardiac events.

Pfizer's Dr. Gandelman declines to comment, but Pfizer in a statement says it "did not -- and never would -- attempt to discourage Drs. Nissen or Topol from publishing their analysis."

Merck's vice president of medical communications, Laurence Hirsch, asked Dr. DeAngelis at JAMA to carry a rebuttal from Merck in today's issue. She angrily refused.

"It was quite extraordinary and almost humorous that the company would do this," says Dr. Topol about Dr. Hirsch's call. Dr. Hirsch declines to comment, but a Merck spokesman says the company simply felt its data should be available to readers simultaneously with the Cleveland Clinic analysis.

The largest Vioxx study analyzed by the Cleveland Clinic authors included 8,076 rheumatoid-arthritis patients treated for up to 13 months with either Vioxx or naproxen, the cheaper pill. Forty-five Vioxx patients suffered a serious, clot-related cardiac event during the study, compared with 20 in the naproxen group. These events included heart attack, unstable angina, cardiac clotting, resuscitated cardiac arrest, sudden or unexplained death, ischemic stroke and transient ischemic attacks, or ministrokes. Such events were 2.38 times as frequent in the Vioxx group as in the naproxen group.

By contrast, in Pharmacia's yearlong study of 8,059 patients, there was "no significant difference" in cardiac events between patients on Celebrex and those taking other low-cost NSAIDs, diclofenac and ibuprofen.

But then the Cleveland Clinic researchers took the unusual step of comparing the rate of cardiac events among Vioxx and Celebrex patients with that in 23,407 medium-risk cardiac patients given placebos, in various heart-attack prevention trials. Statistically, such a step can be iffy, because different study populations may have different heart-attack risks. Still, the doctors concluded the heart-attack rates with Celebrex and Vioxx were high enough to be of concern: The annualized heart-attack rate in placebo patients was 0.52%. With Vioxx, it was 0.74%, and with Celebrex, 0.80%.

"The risk is very low of inducing a heart attack," says Dr. Topol, "but this is tens of millions of people" taking these drugs.

Rheumatoid arthritis may itself increase the risk of heart attack. Most of the patients in the Vioxx study had this disorder, though not those in the Celebrex trial, who mostly had osteoarthritis. Pharmacia's Dr. Geis dismisses the cardiac study's findings, calling the practice of comparing different study populations "inaccurate."

Dr. Nissen acknowledges the study's limitations but says, "We were trying to get an overall impression of what was going on. We think the evidence is there to warrant a lot of scrutiny."

As with any drugs, the risks of the COX-2 inhibitors have to be weighed against their benefits. The study of Vioxx showed that users had half the rate of ulcers and bowel perforations as those taking naproxen. Any drop in the risk of NSAID-related ulcers matters, because estimates are that nearly 100,000 Americans are hospitalized annually for these conditions and as many as 16,500 die of them.

Vioxx's study didn't show that it had eliminated the risk of ulcers, only that it had cut it in half, to 2%. Pharmacia failed to prove any reduction in ulcer risk in its trial -- perhaps because many test patients were also taking aspirin. Celebrex also failed to prove that it reduced pain quickly, something Vioxx studies proved.

The FDA is unlikely to allow either manufacturer to cut or even soften its ulcer warning label, the companies agree. In light of the new data analysis, the agency could even require some warning about the drugs' effect on the heart.

All this is likely to spur managed-care firms' resistance to the drugs, a brewing rebellion that has led to slower sales growth than expected and a June 22 warning that Merck's earnings for the year would be lower than previously announced. Managed-care firms have been dubious that the drugs -- which relieve pain and inflammation no better than far-cheaper pills -- are worth their high prices.

Since 1999, Celebrex and Vioxx have claimed about half of the NSAID market. Sharon Levine, associate executive director of the Permanente Medical Group at Kaiser Permanente, contends that they should be given only to chronic NSAID users who are old, taking steroids or have had ulcers. "Consumers are paying millions and millions for drugs that, for most of them, appear to have no clinical benefit" over much-cheaper pills, Dr. Levine says.

General Motors Corp., which last year spent $47 million providing the two drugs to its employees, believes at least half of those taking the drugs don't need them because they aren't at risk for an ulcer or don't need chronic pain care, says Robert Minton, a spokesman for GM's health-care initiatives.

One big reason for the drugs' popularity is marketing. In the 2001 first quarter, Celebrex and Vioxx were the second and third most heavily advertised drugs in the U.S., each with more ad dollars spent on it than Coca-Cola, according to ad-tracker CMR Inc. Three times the FDA has warned Pharmacia or Pfizer to stop exaggerating Celebrex's benefits to doctors and patients.

Notes

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